Pain and Nociception in Reptiles

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KEYWORDS

- Pain • Nociception • Analgesia • Reptile

CLINICAL APPROACHES TO ANALGESIA IN REPTILES

The analgesic management of reptiles is challenging because of their unique physiologic, anatomic, and behavioral adaptations. As the number of studies examining pain and nociception in reptiles increases, our ability to provide analgesic care improves. The terms pain and nociception are frequently used interchangeably; however, in animals it may be worth differentiating between the 2 terms. Pain is inherently subjective, and is defined as unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, noting that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.[1] Nociception generally refers to the physiologic or neuroanatomical components necessary to sense and transmit the noxious stimuli to the brain where it can ultimately be interpreted as a painful experience (ie, pain). The neuroanatomic components necessary for nociception have been described in reptiles.[2,3] In addition, endogenous antinociceptive mechanisms[3,4] and a demonstrable modulation of nociception with pharmacologic agents known to be analgesics in other species have been established.[5–11] In Tokay gecko lizards (*Gekko gecko*), spinal projections originating in the brainstem region (nucleus raphes inferior) that project to the superficial layers of the dorsal horn have been identified, and these structures suggest the presence of tracts that mediate descending inhibition of nociception, similar to those found in mammals.[8] Neurotransmitters that are important in nociceptive modulation in mammals have been identified in reptiles.[12] Whereas endogenous opioids and opioid receptors involved in reproduction and thermoregulation have been identified in reptiles, there is little known about the role of opioids in nociception.[12–15] This information suggests that at least at the physiologic level reptiles are capable of responding to noxious stimuli in a manner similar to mammals. The ability of reptiles to “feel” pain and the significance of pain or nociception on physiologic homeostasis is an exceedingly complex question requiring integration of both physiologic and behavioral evidence. Until further information is

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The author has nothing to disclose.

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Vet Clin Exot Anim 14 (2011) 45–60
doi:10.1016/j.cvex.2010.09.009

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available, it would seem most ethical for veterinarians to assume that reptiles are capable of feeling pain and to treat or manage pain when there is reasonable evidence that pain is present. In a survey of the membership of the Association of Reptile and Amphibian Veterinarians, 98% of the respondents indicated their belief that reptiles feel pain. However, only 39% of respondents in this survey reported using analgesics in more than 50% or their patients.[16] The reasons for failure to use analgesics were not specifically addressed in this study, yet possibilities include a failure to recognize painful patients, lack of efficacy data, concern regarding adverse effects, and little or no experimentally determined dose or pharmacokinetic information. With increased information available regarding analgesic use in reptiles and with the heightened awareness of the importance of analgesia for zoologic companion animals, it is likely that more veterinarians will provide pain relief to their reptile patients.

The benefits of providing adequate analgesia are well recognized in mammals. The consequences of untreated pain lead to impaired physiologic homeostasis in animals. These alterations can result in negative energy balance, lead to immune system compromise, inhibit healing, and interfere with normal behavioral processes required for health.[17,18]

Preemptive analgesic techniques are also gaining recognition, leading to postoperative pain reduction and preventing and/or limiting the actions of detrimental neurohumoral responses to pain.[19,20] The use of analgesics as part of a balanced anesthetic protocol can reduce the doses of other anesthetics, which can help reduce the negative cardiopulmonary effects of general anesthesia. Overall it has been demonstrated in humans and other mammals that appropriate analgesia is an important part of complete medical care in health and disease.

ASSESSING PAIN IN REPTILES

Appropriate pain management in nonverbal species, including human infants, is an extremely challenging endeavor requiring valid and reliable assessment techniques. Adult humans can express their individual level of pain and its significance to them. In nonverbal humans and animals, behavioral assessment tends to be the best indicator of pain.[21–23] However, with more than 8000 different reptile species identified that exhibit a wide range of unique physiologic and behavioral adaptations, it is exceedingly difficult to assess behavior changes in these animals. This situation makes behavioral alterations associated with pain particularly difficult to identify in reptiles. Recognition of abnormal behavior in reptiles requires careful, often time-consuming observation, and changes may be very subtle. An approach similar to pain assessment in other veterinary species can be adapted for use in reptiles (**Box 1**). If possible, it is best to observe reptiles using a remote camera based on evidence that reptiles may suppress some pain behaviors when an observer is present.[26] This response may be a protective one, similar to that seen in some reptiles subjected to brief physical restraint,[5] and is likely a normal protective behavioral response to a perceived threat, similar to that found in other vertebrate species.[27] A survey of reptile veterinarians found that the anticipated level of pain extrapolated from other species (76%), behavioral changes (66%), anticipated level of pain based on prior experience in reptiles (57%), and physiologic changes (32%) were commonly used to evaluate pain in reptiles.[16]

CHALLENGES OF STUDYING “PAIN” IN REPTILES

Studying most biologic phenomena requires some clearly defined measure of outcome. Studying “pain” is no different except that “pain” is an exceedingly difficult outcome to quantify and define because there is no single gold standard method to quantify pain in veterinary patients or humans.[28] Pain implies an unpleasant sensory or emotional experience and is especially difficult to quantify in patients unable to use language to describe this emotional event, for example, nonverbal humans (ie, pediatrics) or other nonhuman animals. However, as mentioned previously, the inability to communicate does not mean an animal is incapable of feeling pain. Pain reporting in humans is a composite of an individual's interpretation of the nociceptive insult that leads to the painful experience, and is influenced by a myriad of factors (ie, emotional state, concurrent diseases, concurrent medications, prior experience, sex, social status, environmental and economic factors, and so forth).[29–33] It is therefore not uncommon for two individuals subjected to the exact same level of tissue injury to quantify their pain quite differently.[30,33] In veterinary medicine it is probably unrealistic to assume that we can quantify pain in our patients with exact precision, as many of the same factors influencing pain reporting in humans are present when we attempt to interpret pain in our patients.[34–37]

There are many pain scales and questionnaires that have been developed to capture and quantify the individual pain experience for verbal humans. Several of these scales and questionnaires have been rigorously validated and widely adopted for clinical and research use[38]; by contrast, in veterinary medicine we have very few well-validated pain scales. The lack of widely accepted and validated pain scales makes it difficult to interpret conclusions and compare results among animal pain studies.

Pain in animals is most often quantified using semiobjective pain scales. These pain scales are developed using a combination of behavioral and physiologic factors believed to be associated with pain, although most measurable physiologic factors have not been shown to correlate strongly with pain. Pain scales range from very simple visual analog scales (consisting of a line representing the range; no pain to worst pain imaginable) to more complex multivariable numerical ratings scales. Regardless of the specific scale used, all rely on the user to correctly identify pain-related behaviors and/or pain-related physiologic alterations in the patient. Unfortunately, most pain scales are quite context specific and only suitable for assessing a particular type of pain (ie, acute or chronic), and are frequently species specific. Pain scales in veterinary medicine are continually being refined, modified, and tested as our level of sophistication in recognizing and quantifying pain related behaviors improves.

Pain-related behaviors that are crucial for the study of pain and analgesia are not well recognized in reptiles and hence surrogate methods are often required to assess analgesic efficacy. Some techniques attempt to use indirect indicators of analgesia, such as a reduction of the inhalant requirements needed to perform surgery,[39] as evidence of an analgesic effect. However, this technique can be unreliable and should not be used alone to infer analgesic potency.[40]

Another technique commonly used is to measure the response to a noxious stimuli (mechanical, thermal, or chemical threshold testing) with and without a prospective analgesic drug. These responses are most commonly characterized as nocifensive behaviors and as such are believed to be functionally related to pain but not entirely equivalent. This type of testing has been used extensively in mammals for assessing pain and analgesia, and has been shown to correlate well with the clinical efficacy of many drugs.[41,42] However, the predictive validity of these tests with nonopioid drugs is imperfect, and many weaknesses in these models have been described.[42,43] Thermal threshold testing is probably the model most often used for assessing acute nociception in veterinary studies. This technique is nearly ideal, as the noxious stimulus (heat)

Box 1
An approach to pain assessment in reptiles

Behavior

Species Considerations

Requires proper species identification and familiarity with species-specific behaviors. Basic species differences will impact behavioral patterns and these will be important when attempting to differentiate normal from abnormal behaviors.

- Predominant activity pattern (diurnal, nocturnal)
- Predated or predator species
- Habitat (arboreal, aquatic, terrestrial, fossorial)

Individual Patient Considerations

- Stage of ecdysis
  - Some may become more aggressive during this time
- Hibernation status
  - Hibernating animals or those inclined to hibernate may be more docile and less responsive than normal
- Socialization
  - Altered response to human interaction (ie, a normally docile animal biting or poor response to caregiver)
- Concurrent illness
  - Patient may be incapable of exhibiting behaviors associated with pain or behaviors associated with disease may be mistaken for pain behaviors
- Owner assessment
  - Owners are often more familiar with their animals normal behavior, however owners may also be biased based on their own understanding and belief regarding their animals conditions

Environmental Considerations

- Enclosure
  - Home enclosures often more “complex,” compared with hospital enclosures, providing animal with plenty of opportunity to exhibit normal behaviors
- Preferred optimal body temperature observer
  - Ambient environmental temperature is one of the main determinants of metabolic rate in resting reptiles and consequently normal behavior may influenced by alterations in metabolic rate

Locomotor Activity

- Posture
  - Hunched, guarding of affected body area, not resting in normal posture
- Gait
  - Must differentiate neurologic and mechanical dysfunction from pain induced lameness
- Other
  - Excessive scratching or flicking foot tail or affected area
  - Unwillingness to perform normal movements (look up, step up, thrash with tail)
  - Exaggerated flight response

Miscellaneous

- Appetite
  - Reduced appetite may be related to underlying disease but may also be related to pain
- Eyes
  - Species with eyelids may close lids when painful or ill
- Color change
  - Species capable of color change may do so in response to stress and/or pain
- Abnormal respiratory movements
  - May be associated with primary respiratory disease but also pain affecting the muscles and tissues involved in respiration

Anticipated Level of Pain

The anticipated level of pain is commonly used to evaluate pain in reptiles and is based on the likelihood and severity of tissue trauma associated with a particular procedure or condition. This is a well-accepted approach in veterinary medicine, particularly when dealing with less familiar species.[24,25] However, in addition to significant species differences, significant individual differences in response to therapy and response to tissue trauma can be seen

Physiologic Data

Most physiologic parameters have been shown to be relatively poor indicators of pain in most species. Physiologic parameters can be influenced by disease and excitement. In addition, the physiologic parameters of reptiles may be influenced by several metabolic processes such as activity level, temperature alterations, and feeding

Response to Palpation

In some species a negative response to palpation can be a useful indicator of pain. However, in reptiles this may be less sensitive as most reptiles will withdraw from touch regardless of whether the animal is experiencing pain

is readily applied and removed, the latency is easily quantifiable, the behavior is explicit (the animal either does or does not withdraw from the stimulus), and the animal can immediately escape the noxious stimuli.[44] Thermal threshold testing has been used frequently in reptiles to assess the efficacy of various opioids, with very intriguing results.[6,7,9–11,26] However, reptiles are ectothermic, and the use of thermal threshold testing as an index for analgesic efficacy in reptiles raises some interesting questions. For example, would thermal thresholds change between a warming versus a cooling period in reptiles? Why are thermal burns so prevalent among captive reptiles? Could the intrinsic "drive" to warm increase thermal latency independent of drug? Would reptiles adapted to extreme environments (ie, desert animals experiencing hot days and cold nights) be more tolerant of heat than species normally inhabiting more temperate environments? It is possible that thermal latency in reptiles is affected by their thermal status (cooling, warming) and natural environmental adaptations. As thermal threshold testing is used more frequently to assess analgesic responses in reptiles, the application and strength of this method in ectothermic animals will be better understood.

Reptiles, unlike other commonly studied domestic animals such as dogs and cats, are not a single species; rather, they collectively represent more than 8000 species belonging to 4 distinct Orders: Crocodilia (crocodiles, alligators, caimans), Sphenodonita (tuataras), Squamata (snakes, lizards), and Chelonia (turtles, tortoises). The diversity among this population of animals makes it very difficult to make broad generalized recommendations for the entire group. Even among the limited number of reptile studies performed using very similar experimental techniques, marked differences in anesthetic requirements[39,45] and analgesic efficacy[9,10] have been observed.

Despite the challenges inherent in studying pain in reptiles, familiarity with normal behaviors of our reptile patients, using a systematic approach to evaluating pain and through the thoughtful use of information obtained from scientific studies we can greatly improve the overall comfort of our patients experiencing nociception and pain.

ANALGESIC THERAPY IN REPTILES

A carefully designed analgesic plan should include the specific analgesic drugs, route of drug administration, steps to monitor patient response to therapy and to address the provision of ongoing supportive patient care. Significant pharmacokinetic and pharmacodynamic differences exist between reptiles and mammals, making the extrapolation of drug dosing difficult. When available, species-specific analgesic drug studies in reptiles provide valuable insight to help guide analgesic therapy. However, critical evaluation is required to accurately interpret the results of these studies.

ROUTE OF DRUG ADMINISTRATION

The route of drug administration is an important consideration in reptiles for many reasons, including ease of administration, unique anatomic or physiologic structures, and variability in drug bioavailability and uptake among the various routes of drug administration.

Intravenous drug administration is the most predictable method for delivering a drug systemically. Intravascular injection ensures complete bioavailability of a drug and may avoid the tissue irritation associated with some drugs when given intramuscularly or orally. However, intravenous drug administration is not always feasible in reptiles but the combination of good technique, practice, appropriate patient selection, and skilled physical restraint can facilitate predictable venous access.

Intramuscular drug administration is a more convenient route for drug administration than the intravenous route but may be associated with reduced bioavailability. A study using green iguanas (*Iguana iguana*) found the bioavailability of ketoprofen when administered intramuscularly was 78%, representing a 28% reduction in bioavailability.[46] Historically, drug administration into the hind limb and tail has been avoided because of concerns about renal first-pass effect and renal toxicity associated with venous drainage into the renal portal system. In some species, this may be more of a theoretical than practical concern, as only a small amount of blood from the hind limbs and tail passes through the kidney,[47,48] whereas in other species a small amount from the hind limbs passes through the renal portal system while substantial amounts of blood from the tail passes through the renal portal system.[49] Therefore it may be best to avoid hind limb and tail administration of potentially nephrotoxic drugs or those highly metabolized or excreted by the kidneys, such as nonsteroidal anti-inflammatory drugs (NSAIDs). Another important consideration, less often discussed, is the possibility of a significant hepatic first-pass effect following hind limb drug administration. Anatomic studies performed in red-eared sliders showed that the femoral veins drained directly into the liver via the abdominal vein, creating ideal circumstances for significant presystemic hepatic extraction of drugs consequently leading to reduced drug bioavailability.[48] This hypothesis is supported by a recent study reporting approximately 70% relative bioavailability of buprenorphine injected into the hind limb versus the forelimb.[50] This finding is an important one because most opioids are susceptible to significant hepatic extraction,[51] further supporting the recommendation to preferentially use the forelimbs for drug administration.

Oral drug administration may be more desirable for patients who require chronic analgesic therapy, as most reptiles will become intolerant of repeated intramuscular injections. Oral drug administration can be difficult in some reptile patients, although the use of feeding tubes can markedly simplify and facilitate this process. An important consideration is the significant differences in gastrointestinal function among reptile species. Many are strict carnivores (snakes) and may fast for days to months between meals, whereas others are primarily herbivores (turtles, tortoises, and some lizards) and tend to feed more or less continuously. These differences would presumably affect the bioavailability and pharmacokinetics of drugs given orally among the different reptile species. However, a study in green iguanas found that the bioavailability and pharmacokinetics of meloxicam given orally was essentially the same as intravenous administration.[52]

DRUGS

There are 3 primary classes of analgesic drugs used in reptiles: opioids, local anesthetics, and NSAIDs (**Table 1**).

Opioids

It is well documented that reptiles have opioid receptors in the central nervous system[12,13] and that the proopiomelanocortin system (1 of the 3 molecular systems from which all naturally occurring opioids are derived) is well preserved among vertebrates.[63,64] The importance of the different opioid receptors in modifying nociception is far less clear and although increasing numbers of studies examining the role of opioids in reptile nociception are becoming available, each study should be carefully evaluated for the quality of experimental design and strength of its conclusions. Not surprisingly, the results of these studies suggest that the role of various opioid receptor agonists may vary among the reptile orders and even among species.

Butorphanol is a kappa-opioid receptor (KOR) agonist and mu-opioid receptor (MOR) antagonist, and is generally considered to be a mild analgesic in most veterinary species.[51] Similarly in reptiles, butorphanol, despite its frequent use,[16] does not appear to produce evidence of significant antinociceptive effects in all reptiles.[9,10,26,39,65] However, some studies suggest that certain doses of butorphanol in certain species may provide antinociception.[10,53] In one study, the intensity of motor reactions in response to an electrical stimulus applied to the tails of green iguanas was reduced.[53] However, the intensity of motor reactions was a subjectively evaluated parameter and may confound results. In another study, butorphanol administered at exceedingly high clinical doses (20 mg/kg intramuscularly) appeared to possess thermal antinociceptive properties in corn snakes, whereas using the same experimental model it failed to produce evidence of antinociception in bearded dragons (*Pogona vitticeps*)[10] and red-eared sliders (*Trachemys scripta elegans*).[9] Finally, in an experimental model using specific opioid receptor agonists, a pure KOR agonist failed to produce evidence of thermal antinociception in red-eared slider turtles.[11] Based on the accumulated data to date concerning butorphanol and its antinociceptive effects in reptiles it would seem that, at best, butorphanol may produce some antinociceptive effects at very high doses and that its clinical efficacy is highly questionable.

Table 1
Dosages of drugs with potential analgesic effects in reptiles

Drug	Dose (mg/kg)	Route	Interval (hours)	References	Comments
Opioids					
Butorphanol[a]	1.0–2.0	IM	NA	[9,10,39,53,54]	May not be effective as an analgesic in reptiles even at excessive doses
Buprenorphine	0.005–0.02 0.075–0.1	IM, IV, SC	NA	[50,53,54]	Analgesic effect not clearly demonstrated Pharmacokinetics have been determined in red-eared sliders Evidence of enterohepatic recycling
Morphine	0.05–4.0 (crocodiles) 1.5–6.5 (turtles) 1.0 (green iguanas)	IC, IM	NA	[5,7,9,10,53,54]	May require several hours to reach peak effect Duration of action may persist up to 24 h in turtles Significant respiratory depression in turtles
Meperidine	1.0–5.0	IC	NA	[7,54,55]	
Tramadol	10–25 10	PO SC	NA	[56]	Oral dose increased thermal nociceptive latency between 6 and 96 h SC dosing increased thermal nociception latency between 12 and 48 h Less respiratory depression than that from morphine

NSAIDs					
Carprofen[a]	1.0–4.0 followed by 1.0–2.0	IM, IV, SC	24–72[b]	[54,55]	
Flunixin meglumine[a]	0.1–2.0	IM	24–48[b]	[54]	
Ketoprofen	2.0	IM, SC	24–48[b]	[46,54,55]	PK determined for IM and IV administration
Meloxicam	0.1–0.2	IM, IV, PO	24–48[b]	[52,54]	PK determined for oral and intravenous administration in green iguanas Evidence of enterohepatic recycling
Other					
Ketamine	<10	IM, IV, SC	NA	[54]	Low doses <10 mg/kg likely associated with analgesia without sedation
Medetomidine	50–100 μg/kg (tortoises) 150–300 μg/kg (aquatic) 150 μg/kg (snakes and lizards)	IM, IV, IO	NA	[54,57–61]	Lower doses may be effective for analgesia
Xylazine[a]	1–1.25	IM	NA	[54]	
Bupivacaine (0.5% or 0.25%)[a]	Toxic dose unknown, recommend <2 mg/kg	Local infiltration	NA	[54,62]	Dilute to 0.125% to increase volume
Lidocaine (2% or 1%)[a]	Toxic dose unknown, recommend <5 mg/kg	Local infiltration	NA	[54,55]	Dilute to 0.5% to increase volume

Abbreviations: IC, intracutaneous; IM, intramuscular; IV, intravenous; NA, interval dosing data unavailable, based on duration of clinical effect; PO, by mouth; SC, subcutaneous.

[a] Doses not determined experimentally, extrapolated or anecdotal.

[b] Dosing interval based on extrapolation.

Buprenorphine is a semisynthetic partial MOR agonist opioid with unique binding characteristics leading to a delayed onset and a long duration of action in mammals.[51] In the green iguana, buprenorphine did not significantly alter motor reactivity in response to an electrical stimulus when compared with saline.[53] However, these results may be unreliable owing to methodological limitations of the model and the markedly slower onset of action of buprenorphine compared with other opioids. The pharmacokinetics of buprenorphine have been determined in red-eared sliders and based on the results, a dosage of 0.075 to 0.1 mg/kg given subcutaneously in the forelimb would maintain plasma drug concentrations at levels associated with analgesia in humans for at least 24 hours in 90% of red-eared sliders.[50] Of note, in the same study evidence of reduced buprenorphine bioavailability was evident when the drug was administered in the hind limb compared with the forelimb. The bioavailability of buprenorphine following hind limb drug administration was 70% relative to forelimb drug administration. The reduced bioavailability was speculated to be the result of a hepatic first-pass extraction effect. The investigators also observed a secondary peak in plasma buprenorphine concentration occurring at around 72 hours following drug administration.[50] This secondary peak may be the result of enterohepatic recirculation, a phenomenon that has been detected in several other species.[66]

Morphine is a MOR agonist opioid with potent analgesic activity in most veterinary species and normally associated with minimal respiratory side effects when used at clinical doses.[51] However, the respiratory depression associated with MOR agonists can be exaggerated when combined with inhalant anesthetics and other sedatives.[51] There is considerable evidence that morphine may be effective as an analgesic in at least some reptile species.[6,7,9,10,53] It should be noted that time for onset of action appears to be prolonged (2–8 hours) following morphine administration, and the duration of effect may vary considerably among species.[6,7,9,10] This process may be related to slow receptor-binding kinetics or slow absorption from the intramuscular or subcutaneous injection site.

Tramadol is an atypical synthetic opioid with weak MOR agonist activity and inhibitory effects on neuronal reuptake of norepinephrine and serotonin.[51] Recent studies involving tramadol suggest it may be an effective long-lasting oral analgesic in reptiles. In red-eared sliders, tramadol administered orally (10–25 mg/kg) and parenterally (10 mg/kg) increased thermal nociceptive latency between 6 and 96 hours and 12 and 48 hours, respectively.[56]

Opioids appear to be safe for use in reptiles, even when relatively high doses are used, producing no discernible alterations in heart rate or behavior (sedation or excitement), but the MOR agonists (morphine) do cause significant respiratory depression in some species.[9,11,67,68] Conversely, opioids such as butorphanol and tramadol seem to be associated with less adverse respiratory effects.[9,11,56] In experimental studies with red-eared sliders using specific opioid receptor agonists, the respiratory depressant effects of opioids appeared to be mediated primarily via MOR and to a lesser extent via delta-opioid receptors (DOR).[69] However, the exact clinical significance of the respiratory depression described is not clear, as reptiles are well known to tolerate prolonged periods of hypoxia.[70–72] Nonetheless, it is prudent to support respiratory function in reptiles exhibiting profound respiratory depression.

Local Anesthetics

Local anesthetics act by interrupting transmission of sensory and motor neurons. In reptiles, local anesthetics are commonly used to facilitate minor surgical interventions but can also be used as local analgesics. Recently a technique has been described to block the mandibular nerve in crocodilians.[73] The limited duration of analgesic effect and accompanying motor paralysis associated with local anesthetics limit their use primarily to the immediate perioperative period or when hospitalized. Local anesthetic toxicity can be avoided by careful attention to total dose of local anesthetic administered to a patient. Many reptile patients are very small, and large doses can accidentally be administered. In general, the toxic doses of local anesthetics in mammals (dogs) should not be exceeded: lidocaine (toxic dose 10–22 mg/kg) and bupivacaine (toxic dose 5 mg/kg).[74] In addition, excessive dilution of local anesthetics may decrease their efficacy. To avoid reductions in efficacy, commercially available concentrations of local anesthetics should probably not be diluted more than 50%.[75,76] One percent lidocaine solution and 0.25% bupivacaine solutions are available commercially, and may be preferred for use in small patients at greater risk for local anesthetic toxicity.

NSAIDs

The role of cyclooxygenase in the pathophysiology of pain and inflammation of reptiles has not been studied. However, clinical reports support the efficacy of NSAIDs in reptiles, and they continue to be widely used.[16] There is only one study attempting to evaluate the analgesic efficacy of NSAIDs in reptiles, and the investigators found no decrease in the physiologic stress responses of ball pythons (*Python regius*) to surgery when meloxicam (0.3 mg/kg, intramuscular) was administered, suggesting it did not provide adequate analgesia.[65] However, it should be highlighted that even in the control animals given only saline there was little or no evidence to suggest that a stress response developed following their surgical procedure, and it was therefore difficult to assess whether meloxicam had an effect on diminishing the stress response.[65] The investigators acknowledge that the stress response was modest compared with that found after simply handling black racers (*Coluber constrictor*),[77] and although they make minimal comment, differences in technique could account for these discrepancies.

Meloxicam is probably the most widely used and recommended NSAID for reptiles. In pharmacokinetic studies, meloxicam administered orally to green iguanas had excellent bioavailability.[52] The results suggest that plasma concentrations associated with analgesia in other species are maintained in iguanas for 24 hours after a single oral dose of 0.2 mg/kg. Yet it should be noted that plasma concentrations of NSAIDs do not directly correspond to the clinical effect, and thus it is difficult to recommend effective and safe dosing intervals. There was also some evidence of enterohepatic or urinary resorption of meloxicam.[52] A pilot examination of the pharmacokinetics of ketoprofen administered intravenously and intramuscularly in green iguanas determined that bioavailability (78%) was decreased when administered intramuscularly and that terminal half-life was greater than in comparable studies in dogs.[46] This finding suggests that dosing intervals in reptiles should be longer than for mammals, a recommendation routinely followed for other drugs in reptiles, especially those associated with significant toxicity. Meloxicam administered daily at doses up to 5 mg/kg orally for 12 days produced no clinically apparent abnormalities or histopathological lesions associated with toxicity. However, mild biochemical and hematological abnormalities were noted that could not be clearly explained.[52] Another study involving daily administration of meloxicam and carprofen to green iguanas for 10 days similarly reported no clinical abnormalities but, did note some minor biochemical and hematological alterations that the investigators considered clinically insignificant.[78] Regardless of the apparent safety of NSAIDs in reptiles, it is advisable to consider the possibility that side effects similar to those seen in mammals (gastrointestinal [GI] irritation, renal compromise, platelet inhibition) may occur in reptiles. Therefore hydration status, concurrent medications such as steroids, presence of coagulopathy, GI disease, and renal disease should all be addressed before administering these drugs.

Other Drugs

Ketamine administered at subanesthetic doses is being used as an analgesic in many mammalian species, but its analgesic potential in reptiles has not been studied. Ketamine alone and used at anesthetic doses is associated with hypertension, tachycardia, bradypnea, and hypoventilation.[79–81] Ketamine may be a useful analgesic adjunct in select cases. The α_2 agonists produce analgesia, sedation, and muscle relaxation in mammals. In reptiles they appears to produce desirable levels of sedation and muscle relaxation. The analgesic effects of α_2 agonists have not been evaluated in reptiles but clinical impressions suggest they may be capable of producing an analgesic effect. Medetomidine induces cardiopulmonary effects in reptiles similar to those seen in mammals: bradycardia, hypertension, and a reduction in arterial oxygen partial pressures.[57,58] Other analgesic drugs and adjuncts such as tramadol, gabapentin, amantadine, the tricyclic antidepressants, various nutraceutical and physical therapy have not been explored in reptiles but may have a role to play as our understanding of nociception, pain, and analgesic therapy in reptiles increases.

SUMMARY

Reptiles are a very unique and diverse class of animals that have developed distinctive mechanisms, not found in most other animals, for managing alterations in body temperature and metabolic rate. An approach to pain management based on our current understanding of reptile physiology, nociception, pain, and analgesia represents a generalized approach to pain management in this class of animals. As our knowledge and understanding increases, it is likely that our approach to pain management in this class of animals will also be modified and refined to more specifically address reptile pain. New information should be evaluated objectively and without the influence of personal bias or beliefs. It is likely that reptiles have evolved unique mechanisms for managing pain and avoiding the negative consequences associated with pain that we do not yet completely understand.

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